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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/636,243	08/10/2000	Bryan S. Wang	8325-1004 (M4-US1)	6438

20855 7590 12/09/2008

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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
12/09/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/636,243	WANG ET AL.	
	Examiner	Art Unit	
	TERESA WESSENDORF	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,6,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-6,20-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/16/08 has been entered.

Status of Claims

Claims 5-6 and 20-21(with respect to the elected species of l0-residue length) are pending and under examination.

Withdrawn Rejections

In view of the amendments to the claims and applicants' arguments the 35 USC 112, first paragraph and 35 USC 102 rejections are withdrawn.

Claim Rejections - 35 USC S 103

Claims 5-6 and 20, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Pomerantz in view of Krylov

[or Marmostein] for the reasons of record based on the Board's decision and reiterated below.

The Pomerantz publication has been described for its disclosure of a zinc finger fused to the naturally occurring dimerization domain extracted from the GAL4 protein. Pomerantz's fusion protein differs from the fusion protein contained in the zinc finger complex of claim 5 by having a naturally occurring dimerization domain, instead Pomerantz points the skilled artisan directly to prior art publications that teach modified dimerization domains. Such domains are non-naturally occurring and "join each other by specific binding," meeting the requirements of the claimed "peptide linkers." See claim 5. In particular, reference 19 (hereinafter"Krylov"), cited by Pomerantz for its studies of the coiled-coil interaction motif, describes "protein design rules that can be used to modify leucine zipper-containing proteins to possess novel dimerization properties." Krylov, page 2850, column i. "33 different leucine zipper proteins containing 27 different systematic combinations of amino acids" were produced. Id., page 2856, column 2 ("Discussion"). See also Fig. IB for a list of exemplary "mutant proteins." Id., page 2850, column 2. The mutant proteins were mixed together under conditions which facilitated dimer formation. By measuring the stability of the dimers formed (id.,

page 2852-53, "Thermodynamic stability"), Krylov was able to demonstrate that certain modified dimers had increased stability and specificity as compared to the unmodified form. ("Novel heteroloqous interactions regulate dimerization specificity .... In the second mixing experiment, the stability of the heterodimer is calculated to be greater than the average of the two homodimer stabilities, thus favoring the formation of heterodimers." Id., page 2856, columns 1-2.) Thus, the element missing from Pomerantz - non-naturally occurring peptide linkers - is supplied by Krylov. The skilled worker would have had a reasonable expectation that Krylov's domains could be utilized to complex zinc fingers to which they are attached in view of Krylov's success in not only modifying their binding activity, but in making it stronger (i.e., more stable). Krylov also teaches dimerization domains having the same sequence, meeting the limitations of clam 6. See e.g., id., page 2856, column i, describing homo- and heterodimers, where the homodimers have "the same sequence." Pomerantz describes dimers between ZFGDI fusion protein, where each fusion contains the same zinc finger. Pomerantz, Abstract ("a dimeric zinc finger protein, ZFGDI"). This meets the requirements of claim 20. In sum, we find that Pomerantz and Krylov disclose all elements of the subject matter recited in claims 5, 6, and 20. For the reasons discussed above,

the skilled worker would have considered these claims obvious in view of Pomerantz's express suggestion to combine its teaching with Krylov (i.e., reference 19), and Krylov's disclosure that would have led the skilled worker to reasonably expect that the combination would work.

Response to Arguments

Applicants assert that the GAL4 dimerization domains described in Pomerantz are not 30 or fewer amino acids in length. Indeed, these domains are twice the size of the claimed peptides, extending from residues 41-100 of GAL4. Thus, Pomerantz does not teach or suggest the claimed complexes.

In response, Pomerantz at least suggests at e.g., paragraph bridging pages 965 and 966 heterologus modules fused with short peptide linker using computer modeling. Such suggestion of a shorter linker than the Gal4 would lead one having ordinary skill in the art to the desirability of a shorter linker. Furthermore as Pomerantz discloses at page 966, second complete paragraph, the dimerization motif does not appear to require species sequences for binding. It would within the ordinary skill in the art to use a short linker to fuse two known zinc finger proteins. The prior art and the specification (page 15, line16) discloses short linkers (5-12 residues) albeit, for

covalent linkage. Thus, whether the short linkers used to fuse two proteins are covalent or non-covalent linkage (dimerization) is immaterial as the prior art teaches or at least suggests the desirability of a short linker. As stated by applicants at paragraph bridging pages 3-4 of the instant REMARKS:

> Dimerization modules of the type reported here may be useful when designing new zinc finger proteins that recognize extended binding sites, **and such modules provide effective alternatives to covalent linkage** (Liu et al. Proc. Natl. Acad. Sci. USA 94, 5525 (1997); Kim et al., Proc. Natl. Acad. Sci. USA 95, 2812 (1998)) **or to the use of coiled-coil dimerization domains** (Pomerantz et al., Biochemistry 37, 965 (1998)). (Emphasis added).

Attention is also drawn to applicants' specification at e.g., page 36, lines 2-12:

> The success of the initial screen, which yielded several different peptides that mediate dimerization, suggests that such peptides are relatively "common" in sequence space. **Zhang et al. (19) have isolated dimerization elements by fusing 5 random fragments** of the yeast genome to the DNA-binding domain of lambda repressor and selecting fusion proteins that reconstitute repressor activity. **This group reached similar conclusions regarding the frequency of functional dimerization domains.** Our finding may help explain why dimerization elements are so common and have such diverse sequences in natural DNA-binding proteins. The peptide that we have isolated may be analogous - in an evolutionary and functional sense - to the peptide extensions that are responsible for heterodimerization of certain homeodomain proteins (20-22). (Emphasis supplied).

Thus, it would be within the ordinary skill in the art at the time the invention was made to employ a linker, covalent or

non-covalent (dimerizing) peptide, in the same fusion complex of zinc finger protein that function in the same way by binding to DNA. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Applicants argue that Krylov does not cure the deficiencies of Pomerantz. Krylov also fails to teach dimerizing peptides of 30 or fewer amino acids in length, choosing instead to perform experiments on mutants of an 80 amino acid leucine zipper "host" protein. See, page 2859, left column, first paragraph of Materials and methods). Krylov is clear that these 80 amino acids "contain the entire bZIP region of the protein." ld. Furthermore, contrary to the Examiner's assertion, Krylov fails entirely to teach or suggest anything about zinc finger proteins complexed together via non-naturally occurring peptides fused to each of the zinc finger proteins. Rather, Krylov discloses only mutation of certain amino acid residues of naturally occurring leucine zipper domains in the context of the naturally occurring dimerization domain (Krylov, left column of page 2850 to left column of page 2851 and Fig. 1): The protein sequence of the first four leucine zipper heptads of the host or parent protein, the bZIP protein VBP (Iyer et al., 1991) is

presented in Figure lB. The lower section of Figure 1B presents the nomenclature used to describe our various mutant proteins. Clearly, Krylov's leucine zipper dimerization mutants are not fusions as claimed. Nor do they comprise a non-naturally occurring dimerizing peptide having a length of 30 amino acids or less, as claimed. Simply put, because each reference teaches dimerization domains of greater than 30 amino acids in length, there is no combination of Krylov and Pomerantz that would result in the claimed complexes that include peptides of 30 or fewer amino acids in length in which are selected from random peptide libraries (rather than mutating naturally occurring dimerization domains).

In reply, applicants' arguments as to the selection of 30 or fewer amino acids in length from random peptide libraries is not commensurate in scope with the claims which does not recite said selection from random peptide libraries. As clearly pointed out by applicants the instant linker has been selected from the numerous linkers included in the alleged random peptide library. To select the optimum linker length, which is disclosed in the art ranging from 5 (albeit for covalent linker) up to 59 (for the non-covalent-dimerization domain, GAL4) would be within the ordinary skill in the art at the time the invention was made.

As held by the majority in Merck & Co. Inc. v. Biocraft Laboratories, Inc., 874 F.2d 804, 10 USPQ 2d 1843 (Fed. Cir. 1989), at 10 USPQ 2d 1846:

> That the '813 patent discloses a multitude of effective combinations does not render any particular formulation less obvious. This is especially true because the claimed composition **is used for the identical purpose taught by the prior art.** See In re Corkill, 771 F.2d 1496, 1500, 226 USPQ 1005, 1008 (Fed. Cir. 1985) (obviousness rejection of claims affirmed in light of prior art teaching that "hydrated zeolites will work" in detergent formulations, even though "the inventors selected the zeolites of the claims from among "thousands of compounds"); In re Susi, 440 F.2d 442, 445, 169 USPQ 423, 425 (CCPA 1971) (obviousness rejection affirmed where the disclosure of the prior art was "huge, but it undeniably include[d] at least some of the compounds recited in appellants generic claims and it is of a class of chemicals to be used for the same purpose as appellant's additives"). (Emphasis added).

Applicants' attention is again drawn to the disclosure of Krylov at e.g., page 2849, the abstract and paragraph bridging col. 1 and col. 2 which describes a repeating helical dimerization interface... a repeating structural unit of two helical turns or **seven amino acids** (a heptad repeat)(reads on less than 30 amino acids of claim 5). (Emphasis added).

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA WESSENDORF whose telephone number is (571)272-0812. The examiner can normally be reached on flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TERESA WESSENDORF/
Primary Examiner, Art Unit 1639